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PATENT & TRADEMARK OFFICE

AMENDMENTS TO THE SPECIFICATION

The Examiner has objected to the specification containing embedded hyperlinks. Applicant hereby amends the appropriate paragraphs of the specification as follows to overcome this objection.

Please replace the paragraph beginning at line 1, page 16 with the following paragraph:

A few positive results were found for residues that are presumed to be just outside the active site, or in the second shell. These residues are Tyr164 in TIM, Glu185 and Lys21 in AR and His135 in PMI. It is undetermined whether these residues have perturbed titration functions because they actually participate in catalysis and/or recognition, or because they are simply physically very close to the area where catalysis occurs. In the latter case, they would presumably be subject to the same pH-dependent potentials as the species that are engaged in catalysis. Three out of four of these residues are conserved (*Gish et al. 1993*). Tyr164 in TIM and His135 in PMI are conserved across a range of species. A ClustalW alignment ~~(http://www.ebi.ac.uk/clustalw)~~ (Thompson et al. 1997) was run for TIM sequences from chicken, human, mouse, *Drosophila melanogaster, Zea mays* (maize) and *Emericella nidulans*. His95, Tyr164 and Glu165 are conserved in TIM from all of these species. A ClustalW alignment (see *supra*) was run for PMI sequences from *Candida albicans,* human, *Saccharomyces cerevisiae, Emericella nidulans,* and *Salmonella typhimurium*. Lys100, His135, Lys136 and Tyr287 are conserved across all of these species. Glu185 in human aldose reductase is conserved over a number of human enzymes with some sequence identity. A ClustalW alignment (see *supra*) alignment was run for sequences of the human enzymes aldose reductase, bile acid binding protein, chlordecone reductase, 3-oxo-5-beta-steroid reductase and aldehyde reductase. Tyr48, Glu185, Lys77 and Tyr107 are conserved across these enzymes. Cys298 and Lys21 are not conserved. Tyr209 is conserved across all of the proteins except chlordecone reductase, where it is replaced by a histidine. This observed conservation lends support to the notion that these residues do play functional roles, e.g., in catalysis, recognition, catalytic efficiency or in the stabilization of the protein fold.

Please replace the paragraph beginning on line 18, page 32, with the following paragraph:

A sequence alignment was performed for plant cysteine proteases from alder, *Arabidopsis thaliana*, barley, ice plant, kiwi, rice, and sweet potato and compared with papain. Sequence searches were preformed using WU-Blast2 ~~http://blast.wustl.edu/~~ [*Gish et al. 1993*] and sequence alignments were performed with ClustalW ~~http://www.ebi.ac.uk/clustalw~~ [*Thompson et al. 1994*]. The overall sequence identity scores for these proteins with papain are in the range 45-51%. Table 4 (shown below) shows the alignment results for all of the residues determined to be anomalous in papain by THEMATICS. Note how all five residues in the two positive clusters are perfectly conserved across the species, but the two isolated anomalous residues, E52 and R96, are not perfectly conserved. E52 is conserved in all but two of the species; R96 is not conserved.